and wherein said formulation maintains a therapeutic plasma concentration of bisoprolol for the remainder of a twenty-four hour period measured from administration.

REMARKS

As an initial issue, Applicants note that the Office Action acknowledged Applicants' Information Disclosure Statement filed June 20, 2002, and included an initialed Form PTO-1449. However, Applicants note that on page 2 of 3, the line showing the Examiner's consideration of the listed documents does not extend completely through the box for W.J. Elliott et al., Blood Pressure Monitoring, 1997, Vol. 2, No. 1, pgs. 53-60. Applicants respectfully request that the Office expressly indicate, in the next Office Action, that the Elliott et al. article was considered.

With the Request for Continued Examination filed June 20, 2002, Applicants canceled claims 2, 9, 26, and 27, amended claims 1, 3-8, 10-25, and 28-30, and added new claims 31-42. Thus, as of June 20, 2002, claims 1, 3-8, 10-25, and 28-42 were pending. This Response does not amend, cancel, or add claims. Thus, claims 1, 3-8, 10-25, and 28-42 are pending.

Claim Rejection - 35 U.S.C. § 103

The Office rejects claims 1, 3-8, 10-25, and 28-42, under 35 U.S.C. § 103(a) as being unpatentable over Oshlack et a. (5,580,578) in combination with Miller et al. (U.S. Patent No. 5,891,471).

With regard to the cited patents, the Office states that:

> Oshlack teaches a sustained release formulation wherein a core of an active agent is coated with sustained release polymer coating. The coating polymer is a copolymer of acrylic and methacrylic esters with a low content of quaternary ammonium groups. These polymers can be pH dependent or independent. The coating can further contain pore formers,

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

> plasticizers and talc. Suitable plasticizers include polyethylene glycols. The cores can be coated with a barrier layer prior to the sustained release coating to separate the therapeutic active agent from the acrylic coating. The cores can also be coated with an overcoat after the acrylic polymer coating is applied. A variety of active agents are contemplated by the reference, including antihypertensives (clonidine, methyldopa). Oshlack does not expressly teach the active agent to be bisoprolol or the exact weight percentages of the polymeric coatings.

(Office Action, page 2, line 22 - page 3, line 9, citations omitted.) The Office then states that:

> Miller teaches that clonidine, methyldopa and bisoprolol are known antihypertensives.

(*Id.*, page 3, lines 10-11.)

The Office argues that "[w]hile the reference does not teach the complete concentration or weight percentage range, differences in concentration or weight percentage will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or weight percentage is critical." (*Id.*, at lines 12-15.) The Office concludes that "it would have been obvious to a person of ordinary skill in the art to prepare a sustained release composition wherein a core of the active agent bisoprolol is coated with [an] ammonio methacrylate polymer and optionally coated with a barrier layer and/or an overcoat." (*Id.*, 19-22.)

Applicants respectfully traverse the rejection. In response to the rejection, Applicants initially note that claims 3-8, 10-25, and 28-42 ultimately depend from claim 1, and thus, include by reference all of its recited elements. Applicants present claim 1, as amended herein, for ease of reference:

> 1. A multiparticulate bisoprolol formulation for once-daily oral administration, said formulation comprising at least two particles comprising a core of bisoprolol or a pharmaceutically acceptable salt

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

thereof, and a polymeric coating, wherein following administration said formulation produces a bisoprolol plasma concentration of not more than about 1 ng/ml for at least about three hours, and thereafter provides a sustained release of bisoprolol that produces a therapeutic plasma concentration not later than about 12 hours following administration, and wherein said formulation maintains a therapeutic plasma concentration of bisoprolol for the remainder of a twenty-four hour period measured from administration.

Applicants respectfully submit that the Office fails to establish a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness, the Office must satisfy three basic criteria. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. (See M.P.E.P. § 2142.) In this instance, the Office has failed to satisfy all three criteria.

In the Action, the Office focuses on the teaching in Oshlack et al. of a sustained release formulation having a core coated with a polymer coating. Applicants admit that claim 1 recites a formulation having, among other things, "a core of bisoprolol," and "a polymeric coating," wherein the formulation provides "a sustained release" component. But to focus on these elements to the exclusion of the other claim elements is to improperly lose sight of Applicants' claimed invention and contribution to the art.

Claim 1 is not only directed to a multiparticulate formulation comprising at least two particles comprising a core and a polymeric coating. It is further directed to such a bisoprolol formulation that, following administration, produces a bisoprolol plasma concentration of not more than about 1 ng/ml for at least about three hours, and

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

thereafter provides a sustained release of bisoprolol that produces a therapeutic plasma concentration not later than about 12 hours following administration, and wherein such formulation maintains a therapeutic plasma concentration of bisoprolol for the remainder of a twenty-four-hour period measured from administration. Claim 1 includes these functional recitations, and the Office has improperly ignored these aspects of Applicants' claimed invention in its rejection of record.

Oshlack et al. clearly does not teach these functional aspects of Applicants' claimed invention. In particular, Applicants' claim 1 recites a biphasic release profile. A first phase, which the claim recites as "[producing] a bisoprolol plasma concentration of not more than three hours," achieves in a delay in appreciable drug release. During this approximately three-hour period following administration, little or no drug is released from the formulation, thereby producing bisoprolol plasma concentrations that do not exceed about 1 ng/ml.

The second phase is a sustained release phase, which follows the first phase. During this second phase, a therapeutic plasma concentration is achieved within twelve hours after administration, and the therapeutic plasma concentration is then maintained for the remainder of a twenty-four-hour period following administration. Applicants' claims very clearly recite that the formulation "provides a sustained release of bisoprolol that produces a therapeutic plasma concentration not later than about 12 hours following administration, and wherein said formulation maintains a therapeutic plasma concentration of bisoprolol for the remainder of a twenty-four hour period measured from administration."

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

A simple reading of the claims makes clear that the functional recitations referred to above are present and required by the claim. As noted above, the Manual of Patent Examining Procedure, not to mention the Federal Circuit, requires that, for a *prima facie* case of obviousness, the prior art reference (or references when combined) must teach or suggest all claim limitations. Oshlack et al. does not teach or suggest the aforementioned function recitations in Applicants' claims. As an example, nothing in Oshlack et al. teaches or suggests a delay in the release of a drug from a formulation.

In fact, all of the formulations exemplified by Oshlack et al. for which results are demonstrated in the Figures, appear to release drug without a delay. For example, each of Figures 3, 4, 5, 6, and 8, present graphical representations of plasma drug levels for formulations according to Examples 13, 14A and 15A, 14 and 15, 16 and 17, and 19 and 20, respectively. Each of these Figures shows a quantifiable plasma level appearing as early as one hour following administration. Oshlack et al. very clearly does not teach or suggest a formulation that exhibits a lag or delay in release, much less the specific lag achieved by Applicants' claimed formulation.

Applicants respectfully submit that claim 1 clearly recites this exemplary element, but that Oshlack et al. just as clearly does not teach or suggest it. However, out of an abundance of concern that the Office has ignored the "lag" element of the claimed invention because it is unclear, Applicants have amended the claim to clarify that the three-hour period during which the bisoprolol plasma concentration does not exceed 1 ng/ml constitutes a "lag" in drug release. Applicants respectfully submit that there can be no question that Oshlack et al. does not teach or suggest at least this element, which already was present in the rejected claim.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

Another requirement of a *prima facie* case of obviousness is an identification by the Office of the motivation to combine or modify references to arrive at the claimed invention. Satisfaction of this requirement is also lacking from the Office's rejection in this instance.

As noted, Oshlack et al. teaches formulations that rapidly achieve a measurable plasma drug concentration. As described above, exemplified formulations from Oshlack et al. appear to achieve those concentrations in an hour or less. Additionally, Oshlack et al. teaches that for a 24-hour formulation, about 0% to about 42% will be released after one hour, about 5% to about 60% after two hours, and about 15% to about 75% will be released after four hours. (Column 12, lines 12-15.) Oshlack et al. clearly suggests formulations that begin releasing drug shortly after administration.

Yet there is nothing in Oshlack et al. that would suggest the addition of a first phase of drug release during which minimal amounts of drug are released. There is nothing that would suggest a lag in release of drug from the formulation following administration. In particular, there is nothing in Oshlack et al. that would suggest a three-hour lag in release of drug from the formulation following administration. In short, there is nothing in Oshlack et al. that would lead to this element of claim 1.

The third requirement for a *prima facie* case of obviousness is that there be an expectation of success from the modification or combination asserted by the rejection. In this instance, that modification would be the addition of a lag phase component to the formulations of Oshlack et al. In this instance, there would be no expectation of success in making that modification, and the Office has not asserted that there would be any success in the modification.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

Nothing in Oshlack et al. suggest, much less explains, how to achieve a period during which little or no drug is released. There is no teaching that explains how to minimize a subject's exposure to the drug immediately following release. There is certainly no teaching that explains how to achieve a lag of at least about three hours. Everything in Oshlack et al. is directed to explaining how to achieve an immediate and extended drug release; nothing in Oshlack et al. explains how to achieve a delay in release before a sustained release period. Thus, as Oshlack et al. provides no teaching, suggestion, or mention whatsoever, of a delay or lag in release, much less a desired one, it cannot possibly impart any expectation of success in such an element.

In summary, Applicants' claim 1 recites a formulation having at least two phases of release: a delay, or lag, phase during which minimal drug is released, followed by a sustained release phase during which therapeutic plasma concentrations are achieved and maintained. Without even addressing whether or not Oshlack et al. teaches or suggests a sustained release phase as claimed, Applicants submit that Oshlack et al. does not teach Applicants' first phase: a delay or lag phase. In particular, Oshlack et al. does not teach or suggest a bisoprolol formulation in which, for at least about three hours following administration, the plasma concentration is not more than 1 ng/ml. Oshlack et al. does not teach or suggest this element of Applicants' claim 1. Moreover, Oshlack et al. does not provide any suggestion or motivation to add such an element to its disclosed formulations, and in the absence of any mention or suggestion of such an element, there is no expectation of success in its addition. For at least these reasons, the rejection for obviousness is improper and should be withdrawn.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

In addition, Applicants note that Oshlack et al. does not teach or suggest the use of bisoprolol. The Office states that "[a] variety of active agents are contemplated by the reference, including antihypertensives (clonidine, methyldopa)." (Office Action, page 3, lines 5-7, citations omitted.) Applicants note that clonidine is a selective α_2 adrenergic agonist. (*Goodman and Gilman's The Pharmacological Basis of Therapeutics, Eighth Edition* (1990), page 208. Chapter 10 of *Goodman and Gilman*, dealing with Catecholamines and Sympathomimetic Drugs, is attached and listed on a Form PTO-1449.) Methyldopa is a centrally acting antihypertensive agent, which is believed to act on central α_2 adrenergic receptors in a manner similar to clonidine. (*Id.* at 210.) Neither of the cited drugs is a β adrenergic receptor antagonist, i.e., "beta-blocker," the class of drugs to which bisoprolol belongs. However, Oshlack et al. does disclose propranolol, a beta-blocker, but suggests that its usefulness is as an "anti-hypotensive," which means a drug that would *increase* blood pressure.

The Office asserts that while Oshlack et al. does not teach bisoprolol as the active agent, Miller et al. (U.S. Patent No. 5,891,471) teaches that clonidine, methyldopa, and bisoprolol are recognized antihypertensives. It may be true that Miller et al. identifies those agents as antihypertensives. However, Oshlack et al. would not lead to the selection of beta-blockers as antihypertensives. As noted above, Oshlack et al. gives only one example of a beta-blocker, and characterizes it as an anti*hypo*tensive agent. If Oshlack et al. provides any guidance relating to the selection of a *beta-blocker*, it is to select one that has anti*hypo*tensive activity. As Miller et al. provides no teaching relating to the antihypotensive activity of beta-blockers, and in particular, to the antihypotensive activity of bisoprolol, it would not lead to the selection of bisoprolol.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

If Oshlack et al. provides any guidance related to the selection of an *antihypertensive*, it would have to be to select examples like clonidine and methyldopa, which, as noted above, are α_2 adrenergic receptor agonists. Indeed, these compounds exhibit an action that is primarily antihypertensive, and these compounds are used primarily for the treatment of systemic hypertension. (*Goodman and Gilman* at 208.) Beta-blockers, in contrast, are used for a number of different cardiovascular conditions, depending on their particular specificity for receptor subtypes. Applicants have attached a review article by Borchard ("Pharmacological Properties of β-Adrenoceptor Blocking Drugs," *J. Clin. Bas. Cardiol.* 1:5-9 (1998)) that discusses the beta-blocker drugs and their pharmacological properties on receptor subtypes.

Beta adrenergic receptor blocking drugs may interact with the β_1 or the β_2 receptor subtype. *Id.* Beta-blockers may be non-specific, i.e., interacting equally with β_1 and β_2 receptors, or they may exhibit specificity for the β_1 subtype. *Id.* Because β_1 and β_2 receptors are expressed to greater or lesser extents in different tissues, these different specificities may result in different pharmacological activities. *Id.* For example, heart tissue beta receptors are 80% β_1 and 20% β_2. *Id.* Blood vessels, on the other hand, express primarily β_2. *Id.* "Drugs without selectivity for β_1-receptors acutely increase peripheral resistance whereas β_1-selective drugs are almost completely without direct vascular actions." *Id.* at 6. Of all of the beta-blockers surveyed in the aforementioned review article, bisoprolol has one of the highest selectivities for β_1-receptor subtypes. (*Id.*, Table 2.)

Oshlack et al. teaches the selection of hypertension agents that are primarily used in treating hypertension, such as clonidine and methyldopa. Because of its β_1-

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

receptor selectivity, bisoprolol would not be selected as the first choice for such a drug. Indeed, Borchard states that "β_1-selective drugs [such as bisoprolol] are almost completely without direct vascular actions." According to Table 2 in Borchard, β_1-receptor selective blockers include acebutolol, atenolol, celiprolol, metoprolol, talinolol, betaxolol, and bisoprolol.

As mentioned above, Oshlack et al. does suggest a beta-blocker, propranolol, but that is for use as an antihypotensive agent. Borchard identifies propranolol as having no β_1-receptor selectivity. (*Id.*, Table 2.) Borchard notes that such drugs "without selectivity for β_1-receptors acutely increase peripheral resistance" (*Id.* at 6), which would explain Oshlack et al.'s classification of the drug as an antihypotensive. Applicants submit that to the extent that Oshlack et al. suggests beta-blockers, it is for their antihypotensive activity. According to Table 2 of Borchard, non-specific beta blockers include bupranolol, penbutolol, sotalol, metipranolol, nadolol, oxprenolol, and propranolol. (*Id.*, Table 2.)

In view of these points, Applicants submit that one would not be motivated to select bisoprolol, based upon reading Oshlack et al. in view of Miller et al. For these reasons, in addition to those set forth above, Applicants respectfully submit that the claimed invention is not obvious over Oshlack et al. in view of Miller et al. and respectfully request the withdrawal of the rejection.

Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: November 5, 2002

By: 

Sean C. Myers-Payne
Reg. No. 42,920
ph. (571) 203-2717
fax (202) 408-4400
sean.myers-payne@finnegan.com

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

APPENDIX TO AMENDMENT

Claim 1 is amended as follows:

1. A multiparticulate bisoprolol formulation for once-daily oral administration, said formulation comprising at least two particles comprising a core of bisoprolol or a pharmaceutically acceptable salt thereof, and a polymeric coating, wherein following administration said formulation exhibits a lag in release, producing [produces] a bisoprolol plasma concentration of not more than about 1 ng/ml for at least about three hours, and thereafter provides a sustained release of bisoprolol that produces a therapeutic plasma concentration not later than about 12 hours following administration, and wherein said formulation maintains a therapeutic plasma concentration of bisoprolol for the remainder of a twenty-four hour period measured from administration.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com